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The quest for equity in liver transplantation: Another lesson learned from women

François Durand*

Hepatology and Liver Intensive Care, INSERM U773, Centre de Recherche Biomédicale Bichat Beaujon CRB3, Hospital Beaujon, University Denis Diderot, Paris 7, Clichy, France

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Compared to time spent on the waiting list which was the main criteria for the allocation of liver allografts a decade ago or less, the MELD score is generally considered a guarantee of transparency, objectivity and equity. Since allografts from deceased donors are a scarce resource, an equitable allocation policy is an absolute prerequisite in liver transplantation. The MELD score is a robust marker of early mortality in cirrhotic patients [1]. This score relies on 3 objective and readily available variables (bilirubin, INR and creatinine) that can be easily updated according to disease progression. Prioritization of patients with the highest MELD score, those who are at higher risk of death without transplantation, was associated with fewer candidates to be added to the waiting list and a decrease in waiting list mortality. Importantly, transplanting the sickest patients did not result in a significant deterioration of post-transplant survival [2]. The MELD score-based allocation policy has been widely adopted in most Western countries.

Even though the MELD score is considered a model of robustness and objectivity, intrinsic limitations have been pointed out. Renal function has a determinant prognostic value in cirrhosis [3]. However, serum creatinine, as a marker of renal function, is a source of inaccuracies and misclassifications. There are several pitfalls in the interpretation of serum creatinine including significant variations over time (especially in patients receiving diuretics) and inter-laboratory variations (especially in patients with jaundice, due to laboratory interactions with bilirubin). Patients with decreased muscle mass, a common finding in cirrhosis, may have falsely low serum creatinine. For the calculation of the MELD score, creatinine values below 1 mg/dl are bounded to 1 mg/dl to avoid negative values after logarithmic transformation. Bounding creatinine to 1 mg/dl is questionable since cirrhotic patients with low creatinine may have markedly impaired renal function [4]. Finally, it was suggested that creatinine might weigh too heavily in the MELD score [5]. Creatinine-based equations are as inaccurate as serum creatinine is. In general, equations tend to overestimate glomerular filtration rate (GFR). Two recent studies have shown that a score incorporating true GFR rather than creatinine or creatinine-based equations would be more accurate than the existing MELD score [4,6]. Unfortunately, direct measurement is technically complex and poorly suited to be repeated at short intervals.

In 2008, a large survey aimed at comparing pre- and post-MELD eras in the United States had shown that, while following the introduction of MELD, race disparities were no longer observed, gender disparities were still present; women being less likely to be transplanted than men [2]. It was speculated that the difference could result from lower muscle mass in women, lower creatinine value for a given GFR and, as a consequence, a lower MELD score. Indeed, others had shown that women with cirrhosis have lower GFR for the same creatinine value, the difference representing a systematic disadvantage for women [7].

In this issue of the Journal of Hepatology, based on a very large series of candidates for transplantation registered in the United States, Myers et al. confirm that under the MELD era, women were still disadvantaged compared to men [8]. By chance, differences between women and men were numerically small in terms of waiting list mortality (11.3% *versus* 10.5% waiting list mortality within 3 months of listing). However, differences were highly significant, probably due to the large size of the study population. Disadvantage predominated in women with a high MELD score (between 21 and 35) while no difference was observed for a score below 21. The results strongly suggest that women disadvantage was due to an overestimation of renal function by creatinine. Indeed, women had significantly lower serum creatinine than men while the two other components of the MELD score, bilirubin and INR, were similar in both groups (except for some MELD strata). An important finding is that in the whole population, the median value of serum creatinine at registration was 1 mg/dl. Therefore, for the calculation of the MELD score, creatinine had to be arbitrarily bound to 1 mg/dl in about 50% of candidates for transplantation. This represents a clear limitation of the MELD score as the assumption that mortality risk relative to renal function would be homogeneous in all patients with serum creatinine less than 1 mg/dl is likely to be wrong. Nevertheless, the proportion of patients in whom creatinine was bound to 1 mg/dl was

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* Hépatologie et Réanimation Hépato Digestive, Hôpital Beaujon, 92110 Clichy, France. Tel.: +33 1 40 87 55 48; fax: +33 1 47 30 44 55.
E-mail address: francois.durand@bjn.aphp.fr

Editorial

higher in women (52%) than in men (42%, $p<0.05$). The authors found that a score including GFR estimated by the modification of diet in renal disease (MDRD) equation (eGFR) was not superior to the existing MELD score in terms of discrimination and calibration, even when serum Na was included. Therefore, using eGFR instead of creatinine would not overcome the disadvantage in women. This finding is not really surprising since eGFR is based on creatinine, and creatinine is an inaccurate marker of renal function in cirrhosis. In theory, taking into account MDRD could help lessen the difference between men and women because the weight given to creatinine in the equation differs according to gender. Taken together, these results clearly show that the weight given to creatinine according to gender in the MDRD equation is not valid in cirrhosis. Unfortunately, this study does not address the issue of whether using true GFR instead of creatinine could make the access to transplantation comparable in men and women. In addition, even if the findings strongly suggest that creatinine was the main cause of disparity between men and women, other factors independent of renal function could play a significant role. Experience shows that small size in women frequently results in more difficult matching between the donor and the recipient. Nevertheless, the present study elegantly highlights that the existing MELD score may be a source of unexpected disparities, that it is not a universal guarantee of equity and that improved accuracy is needed, since equity is a central in liver transplantation. Direct measurement of GFR is the gold standard. However, since it is not suited for routine use, indirect markers and/or equations that accurately assess renal function in patients with cirrhosis are needed to improve prognostic scores.

This study by Myers et al. is based on the United Network for Organ Sharing (UNOS) database, from the United States [8]. Using the UNOS database offers a number of advantages with a very large number of patients coming from different centers. Large cohorts provide high statistical power and accurate adjustments. The database is systematically implemented with new registrants and outcomes are updated. However, the UNOS database also has a number of limitations. The population is limited to the United States and some data (such as ethnicity and distance between donor and recipient) are not necessarily relevant outside the United States. This database has not been designed for the purpose of research alone [9]. Recently, concerns have been raised about inaccuracies and missing data [2]. Importantly, event though the number of patients entered in the database is very large, the number of variables to be analyzed is relatively limited. Again, the purpose is not research. A database, even smaller in terms of population, including more original markers of renal function such as cystatin C and/or measured GFR could help better understand the mechanisms of discrepancies between men and women. The use of the UNOS/OPTN database can be seen as a too easy option for addressing certain issues. It clearly appears that there has been a trend for overexploitation of UNOS/OPTN database-derived studies with more than 130 original studies corresponding to the key words "liver transplantation" and "UNOS and/or OPTN" published between 2000 and 2010 according to the PubMed online library [10]; overexploitation with a limited number of variables to analyze necessary results in redundant publications. Efforts should be made to consider original approaches, even if coming from smaller series, in order to improve knowledge. Efforts should also be made by European and Asian societies to implement multicenter databases and analyze the results.

The concept of a "sickest first" allocation policy, based on the MELD score, has been a major step forward in liver transplantation. Despite objective limitations and many criticisms, the MELD score which gives priority to the sickest patients should not be abandoned. As it is a robust prognostic tool throughout a wide spectrum of liver diseases, further improvement in prognostication will be very difficult to achieve. However, equity in liver allocation will remain central in future years and any improvement, even if modest, is a necessary goal. Improving equity possibly means switching from a very simple allocation policy to a much more complex system taking into account specific conditions and including more subtle adjustments.

The bad news is that women are less likely to be transplanted than men when they are listed for transplantation. But the good news is that for a number of reasons, women are less likely than men to develop end-stage liver disease and/or hepatocellular carcinoma with the need to be listed for transplantation.

References

[1] Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91–96.

[2] Gillespie BW, Merion RM, Ortiz-Rios E, Tong L, Shaked A, Brown RS, et al. Database comparison of the adult-to-adult living donor liver transplantation cohort study (A2ALL) and the SRTR US Transplant Registry. Am J Transplant 2010;10:1621–1633.

[3] Francoz C, Glotz D, Moreau R, Durand F. The evaluation of renal function and disease in patients with cirrhosis. J Hepatol 2010;52:605–613.

[4] Francoz C, Prié D, AbdelRazek W, Moreau R, Mandot A, Belghiti J, et al. Inaccuracies of creatinine and creatinine-based equations in candidates for liver transplantation with low creatinine: impact on the model for end-stage liver disease score. Liver Transpl 2010;16:1169–1177.

[5] Sharma P, Schaubel DE, Sima CS, Merion RM, Lok AS. Re-weighting the model for end-stage liver disease score components. Gastroenterology 2008;135:1575–1581.

[6] Lim YS, Larson TS, Benson JT, Kamath PS, Kremers WK, Therneau TM, et al. Serum sodium, renal function, and survival of patients with end-stage liver disease. J Hepatol 2010;52:523–528.

[7] Cholongitas E, Marelli L, Kerry A, Goodier DW, Nair D, Thomas M, et al. Female liver transplant recipients with the same GFR as male recipients have lower MELD scores – a systematic bias. Am J Transplant 2007;7:685–692.

[8] Myers RP, Shaheen AAM, Aspinall A, Quinn RR, Burak KW. Gender, renal function and outcome on the liver transplant waiting list: assessment of revised MELD including estimated glomerular filtration rate. J Hepatol 2011;54:462–470.

[9] Freeman RB. Transplant data collection: you get what you pay for. Am J Transplant 2010;10:1503–1504.

[10] PubMed. Available at: http://www.ncbi.nlm.nih.gov/pubmed/ (accessed August 2010).